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Meta-analysis on the association between non-steroidal anti-inflammatory drug use and ovarian cancer

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AIM

Animal and *in vitro* studies suggest that the use of non-steroidal anti-inflammatory drugs (NSAIDs) may be associated with reduced risk for ovarian cancer. However, results from these studies have been inconsistent. The aim of our study was to review and summarize the evidence provided by longitudinal studies on the association between NSAID use and ovarian cancer risk.

METHODS

A comprehensive literature search for articles published up to December 2011 was performed. Prior to performing a meta-analysis, the studies were evaluated for publication bias and heterogeneity. Relative risk (RR) or odds ratios (OR) were calculated.

RESULTS

Seventeen reports (13 case–control studies, one clinical trial and three cohort studies), published between 1998 and 2011 were identified. There was no evidence of an association between aspirin use and ovarian cancer risk based on a random-effects model (RR = 0.91, 95% confidence interval (CI) 0.82, 1.01) or a fixed-effects model (RR = 0.94, 95% CI 0.87, 1.01). Similarly, we did not find strong evidence of an association between non-aspirin NSAID use and ovarian cancer using a random-effects model (RR = 0.89, 95% CI 0.74, 1.08) or a fixed-effects model (RR = 0.86, 95% CI 0.76, 0.98). Furthermore, our analysis did not show a strong association between frequency or duration of non-aspirin-NSAID use and ovarian cancer.

CONCLUSIONS

Our findings indicate that there is no strong evidence of an association between aspirin/NA-NSAID use and ovarian cancer. However, this subject deserves further investigation.

Introduction

Ovarian cancer remains the most lethal of the gynaecological cancers and its high mortality rate makes this disease a major health concern. Late diagnosis is one of the main hurdles in the treatment of ovarian cancer, as nearly 70% of women present with an advanced stage of the disease at the time of diagnosis [1]. Therefore, strategies that focus on prevention provide the most rational approach to reducing deaths due to ovarian carcinoma [2].

Epidemiological evidence suggests that ovarian cancer may be related to chronic inflammatory processes. Ness & Cottreau proposed that inflammation of the ovarian epithelium was a pathophysiological contributor to the development of ovarian cancer [3]. Therefore, non-steroidal anti-inflammatory drugs (NSAIDs) are potential agents for

prevention of ovarian cancer. However, findings from these studies have been inconsistent. Some studies reported a risk reduction for ovarian cancer with consumption of NSAIDs [4, 5], while others found no association [4–23] or an increased risk [19, 20]. In 2005, a meta-analysis by Bonovas *et al*. [24] reported that there was no evidence for an association between NSAID use and risk for developing ovarian cancer (random-effects model: RR = 0.92, 95% CI 0.80, 1.06 or a fixed-effects model: RR = 0.93, 95% CI 0.81, 1.06). However, since 2005, eight inconsistent observational studies were subsequently published on the effects of NSAIDs use and ovarian cancer risk [4, 5, 18–23]. Therefore, it is still unclear whether NSAID use can reduce the risk of ovarian cancer and clarification of the potentially chemopreventive effect of NSAIDs is of great significance.

The overall aim of this meta-analysis was to evaluate the association between NSAIDs use (aspirin/non-aspirin-NSAID) and ovarian cancer risk based on all cohort studies, case–control studies, and clinical trials published up until December 2011. Subgroup analyses including a dose–response relationship were also performed.

Methods

Retrieval of published studies

To identify the studies of interest we conducted a computerized literature search. Sources included Pubmed, Web of Science, Medline and Embase. Search terms included: anti-inflammatory agents, aspirin, non-steroidal anti-inflammatory drugs, or NSAIDs combined with ovarian neoplasm, ovarian cancer or ovarian malignancy. The titles and abstracts of the studies identified in the computerized search were scanned to exclude any studies that were clearly irrelevant. The full texts of the remaining articles were read to determine whether they contained information on the topic of interest. The reference lists of articles with information on the topic were reviewed to identify citations to other studies of the same topic. Reference lists of review articles were also inspected to determine relevant publications for completeness of our list of publications.

Inclusion and exclusion criteria

A study was included if it fulfilled the following criteria: (i) was designed as a cohort study, case–control study or clinical trial, (ii) evaluated exposure of NSAIDs or aspirin; and (iii) had an outcome with ovarian cancer incidence. Studies without raw data about exposure and measurements were excluded. In the subgroup analyses, studies that did not provide more detailed information about dose–response effects were eliminated. Studies were also excluded if they included subjects who were enrolled in other, more inclusive studies. In studies with multiple publications from the same population, only data from the most recent publication were included in the meta-analysis, with reference in the text to the older publications. Inclusion was not restricted by study size.

Date extraction

Data were extracted by two independent reviewers using the same standardized form. Discrepancies were settled through additional reviews until a consensus was reached. Information obtained from each study included first author, year of publication, study design, types of NSAIDs, definition of exposure, characteristics and the number of subjects in the exposure and non-exposure groups, duration and frequency of exposure and RR/OR with 95% CI.

Statistical analysis

Studies were grouped by the type of medicine (aspirin or non-aspirin NSAIDs). Two techniques were used to estimate the pooled RR estimates, the Mantel–Haenszel method [25] assuming a fixed-effects model and the DerSimonian–Laird method [26] assuming a random-effects model. The fixed-effects model leads to valid inferences about the particular studies that have been assembled and the random-effects model assumes that the particular study samples were drawn from a larger pool of potential studies and leads to inferences about all studies in the hypothetical population of studies. If heterogeneity is not present, the fixed-effects and the random-effects models provide similar results. When heterogeneity is found ($P < 0.05$), both models may be biased [25, 26].

Publication bias was evaluated using the funnel graph, the Begg & Mazumdar adjusted rank correlation test [27] and the Egger regression asymmetry test [28]. The Begg & Mazumdar test is a statistical analogue of the visual funnel graph. It determines whether there is a significant correlation between the effect estimates and their variances. The absence of significant correlation suggests that the studies have been selected in an unbiased manner. The Egger regression asymmetry test tends to indicate the presence of a publication bias more frequently than the Begg approach. It detects funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the standardized-effect estimates against their precision [24].

To evaluate whether the results of the studies were homogeneous, we used Cochran's *Q*-test. We also calculated the I^2 quantity [29], which describes the percentage variation across studies that is due to heterogeneity rather than chance. I^2 lies between 0% and 100%. A value of 0% indicates no observed heterogeneity and larger values indicate increasing heterogeneity [29].

Data were stratified into subgroups based on study design to examine the consistency across varying study designs with different potential biases. Homogeneity was assessed overall and within this stratification.

To assess any association between NSAIDs doses and the risk of ovarian cancer, drug exposure was grouped as

'regular' and 'irregular'. 'Regular use' was the most common exposure and 'irregular use' was the least common, as reported in the individual studies.

To assess any association between duration of NSAID use and the risk of ovarian cancer, we used the available data from studies in which the duration was >5 years.

All *P* values are two-tailed. For all tests, a probability level < 0.05 was considered statistically significant. STATA 11.0 software was used for the statistical analyses (STATA Corp., College Station, TX, USA).

Results

Search results

Cohort, case–control and clinical studies of NSAID use and ovarian cancer are described in Table 1. We identified five cohort studies, 15 case–control studies and one clinical trial reporting on NSAID use related to risk of ovarian cancer. Two cohort studies, which adopted a standardized incidence ratio (SIR) to estimate RR, were eliminated. SIR is the ratio of observed to expected cases, based on reference incidence rates for the general population [14, 15]. Two studies were excluded from the meta-analysis because we did not want to include multiple publications from the same population [6, 30]. We included a total of 17 studies, with 10 373 cases, in the meta-analysis (Table 1, Figure 1). Of the 17 studies, seven estimates reported statistical significance and nine studies reported a non-significant RR/OR that was ≥1. The ORs for NSAID/aspirin use in the 13 included case–control studies ranged from 0.6 to 1.2 (Table 1).

Seventeen studies evaluated exposure to aspirin and ovarian cancer risk. Seven of the 17 evaluated the relationship between exposure to non-aspirin NSAID and ovarian cancer risk.

Sixteen studies [4–13, 16, 18–22] used newly diagnosed ovarian cancer as a case definition and were controlled for potential confounding factors (at least for age), through matching or adjustments.

All case–control studies used non-cancer controls. Among them, one study [11] used two control groups, one cancer and one non-cancer group. However, we included the RR estimates derived from the analysis on non-cancer controls. The majority of the studies were conducted in the USA [4–8, 10–12, 16, 17, 19–23]. However, some were carried out in the UK [13], Australia [18] and Europe [9]. The publication dates of the included studies ranged from 1998 to 2010. Study designs, along with the estimated RR and 95% CIs are shown in Table 1.

Meta-analysis of exposure to aspirin

Thirteen case–control studies [4, 5, 7–11, 13, 18–22], three cohort studies [12, 16, 23] and one clinical study [17] evaluated exposure to aspirin and ovarian cancer risk.

The funnel plot had the expected funnel shape (Figure 2A). The *P* values for the Begg & Mazumdar test and Egger test were $P = 0.592$ and $P = 0.178$, respectively, both suggesting a very low probability of publication bias. In contrast, Cochran's Q-test had a *P* value of 0.046 (Q = 26.6 on 16 degrees of freedom) and the corresponding quantity I^2 was 39.8%, both indicating heterogeneity among the studies (Table 2).

The association of aspirin use with ovarian cancer was not statistically significant based on the fixed-effects (RR = 0.94, 95% CI 0.87, 1.01) or the random-effects models (RR = 0.91, 95% CI 0.82, 1.01) (Table 2).

After stratifying the data into subgroups based on study design, we found no association between aspirin use and ovarian cancer, in case–control studies (random-effects model, RR = 0.94, 95% CI 0.87, 1.02) or among cohort studies (random-effects model, RR = 0.92, 95% CI 0.77, 1.09) (Table 2). Figure 3 graphs the RRs and 95% CIs from the individual studies and the pooled results.

To analyze the association between dose of aspirin and the risk of ovarian cancer, drug exposure was categorized as 'regular' and 'irregular'. 'Regular use' had the highest and 'irregular' had the lowest frequency of drug use, as reported in the individual studies (Table 3). Seven studies [4, 11, 12, 16, 18, 20, 23] were included in this analysis. There was no statistically significant difference between the calculated pooled RR estimates for the 'regular' and 'irregular' use of aspirin and unity (Table 2), providing little evidence for a dose-dependent relationship between the frequency of aspirin use and risk of ovarian cancer.

To assess any association between duration of aspirin use and the risk of ovarian cancer, we used the available data from studies in which the duration was >5 years. Once again, the calculated pooled RRs for prolonged duration of use were compatible with 1.0 (Table 2), providing little evidence of an association between the duration of aspirin use and risk of ovarian cancer.

Meta-analysis of exposure to non-aspirin NSAID

Four case–control studies and three cohort studies evaluated exposure to non-aspirin-NSAID and ovarian cancer risk.

The funnel plot did not have the expected funnel shape. The underside corner of the pyramidal part of the funnel, which should contain small studies reporting negative or null results, was missing (Figure 2B). The *P* values for the Begg & Mazumdar test and the Egger test were $P = 0.051$ and $P = 0.125$, respectively, both suggesting a very low probability of publication bias. In contrast, Cochran's *Q*-test had a *P* value of 0.089 (Q = 11 on six degrees of freedom) and the quantity I^2 was 45.4%, both indicating heterogeneity among the studies (Table 2).

The association between non-aspirin-NSAID use and ovarian cancer risk was marginally statistically significant based on a fixed-effects model (RR = 0.86, 95% CI 0.76,

Table 1

Studies included in the meta-analysis

Study, Year	Design	Case	All subjects	Exposure	Exposure definition	RR/OR (95% CI)	Adjustments
Cramer *et al.* 1998 [7]	Case–control	563	1 086	Aspirin Non-aspirin-NSAIDs	≥1 times per week for ≥6 months	0.78 (0.53, 1.15) 1.2 (0.74, 1.95)	1, 3, 8, 17, 19, 20, 21
Rosenberg *et al.* 2000 [8]	Case–control	780	5 373	Aspirin NSAIDs	≥1 days per week for ≥6 months	0.8 (0.5, 1.2) 0.7 (0.5, 1.0)	NA
Tavani *et al.* 2000 [9]	Case–control	749	1 647	Aspirin	regular aspirin use for ≥6 months	0.93 (0.53, 1.62)	NA
Akhmedkhanov *et al.* 2001 [10]	Case–control	68	748	Aspirin	≥3 times per week for ≥6 months	0.60 (0.26, 1.38)	3, 8, 13, 14
Moysich *et al.* 2001 [11]	Case–control	547	1 094	Aspirin	≥1 times per week for ≥6 months	1.0 (0.73, 1.39)	1, 15, 11, 8, 16, 14
Fairfield *et al.* 2002 [12]	Cohort	333	76 821	Aspirin Non-aspirin-NSAIDs	≥1 times tablet per week for ≥6 months	1.0 (0.8, 1.25) 0.60 (0.38, 0.95)	1, 3, 7, 8, 9, 10, 11
Meier *et al.* 2002 [13]	Case–control	483	1 877	Aspirin NSAIDs	≥1 prescription	0.1 (0.02, 1.0) 1.1 (0.6, 1.8)	7, 9, 12
Lacey *et al.* 2004 [16]	Cohort	116	31 364	Aspirin Non-aspirin-NSAIDs	Once a week – once a day for at least 1 year	0.86 (0.52, 1.4) 1.0 (0.60, 1.8)	1, 2, 3, 4, 5, 6
Schildkraut *et al.* 2006 [4]	Case–control	586	1 213	Aspirin NSAIDs	Any use	0.63 (0.39, 1.02) 0.72 (0.56, 0.92)	1, 2, 3, 11, 14, 17, 23, 31, 32, 33, 34, 35
Cook *et al.* 2005 [17]	Clinical trial	129	39 876	Aspirin	100 mg every other day	0.95 (0.68–1.35)	None
Merritt *et al.* 2008 [18]	Case–control	1576	1 509	Aspirin NSAIDs	Any use over the past 5 years	1.06 (0.92, 1.23) 0.88 (0.76, 1.02)	1, 3, 8, 17
Hannibal *et al.* 2008 [19]	Case–control	812	2 125	Aspirin NSAIDs	≥5 days per month for ≥6 months	1.2 (0.9, 1.5) 1.2 (1.0, 1.4)	1, 3, 18, 22, 23
Wernli *et al.* 2008 [5]	Case–control	487	3 140	Aspirin NSAIDs	≥2 times per week for 6 months	0.73 (0.54, 1.00) 0.74 (0.59, 0.92)	1, 4, 5, 18, 11, 24, 25
Wu *et al.* 2009 [20]	Case–control	609	688	Aspirin Non-aspirin-NSAIDs NSAIDs	≥2 times per week for ≥1 month	1.49 (0.94, 2.35) 1.56 (0.95, 2.56) 1.62 (1.11, 2.39)	1, 3, 4, 5, 8, 11, 14, 17, 19, 28
Pinheiro *et al.* 2010 [21]	Case–control	1353	3 176	Aspirin NSAIDs Non-aspirin-NSAIDs	≥2 tablets per week for ≥6 months.	0.84 (0.68, 1.04) 0.85 (0.71, 1.02) 0.79 (0.62, 1.01)	1, 3, 5, 8, 11, 21
Lurie *et al.* 2010 [22]	Case–control	1025	1 687	Aspirin Non-aspirin-NSAIDs	≥1 times per week for ≥6 months.	0.84 (0.66, 1.08) 0.79 (0.62, 1.01)	1, 2, 3, 4, 10, 14, 17
Prizment *et al.* 2010 [23]	Cohort	157	20 000	Aspirin Non-aspirin-NSAIDs	Any times per week	0.77 (0.54, 1.10) 0.89 (0.64, 1.23)	1, 7, 23, 25, 26, 27

1, Age; 2, ethnicity; 3, duration of oral contraceptive use; 4, family history of ovarian cancer; 5, menopausal status; 6, duration of oestrogen use; 7, body mass index; 8, parity; 9, smoking; 10, postmenopausal hormone use; 11, tubal ligation history; 12, paracetamol (acetaminophen) use; 13, age at menarche; 14, first degree family history of breast cancer before age 50 years; 15, age at first birth; 16, presence of irregular menses; 17, education; 18, county of residence; 19, religion; 20, menstrual pain, headache, arthritic pain; 21, study centre; 22, calendar year; 23, number of full-term pregnancies; 24, year of interview; 25, history of heart disease; 26, partial oophorectomy; 27, HRT use; 28, talc use; 29, gender; 30, alcohol and coffee consumption; 31, months of breastfeeding; 32, history of endometriosis; 33, pelvic inflammatory disease; 34, hysterectomy; 35, severe menstrual cramping.

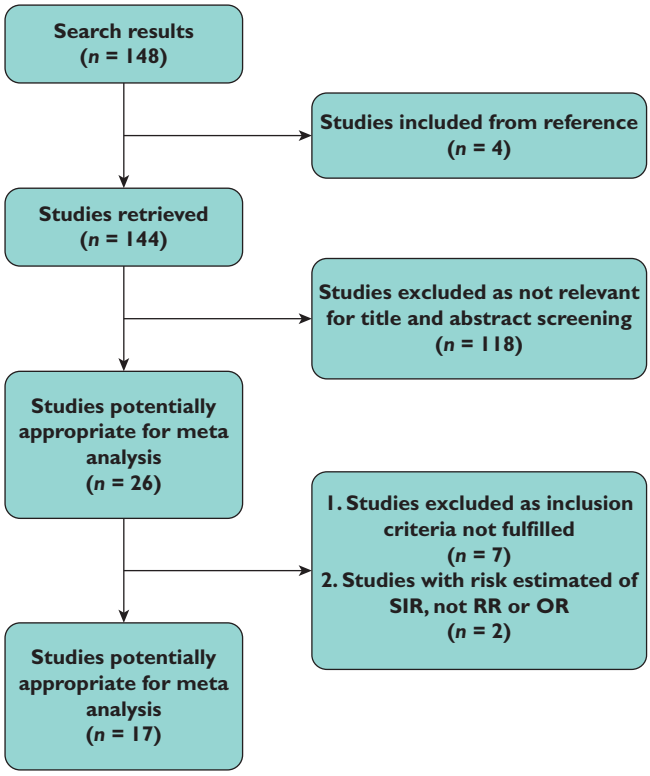

Figure 1

Selection process (SIR, standardized incidence ratio; RR, relative risk; OR, odds ratio)

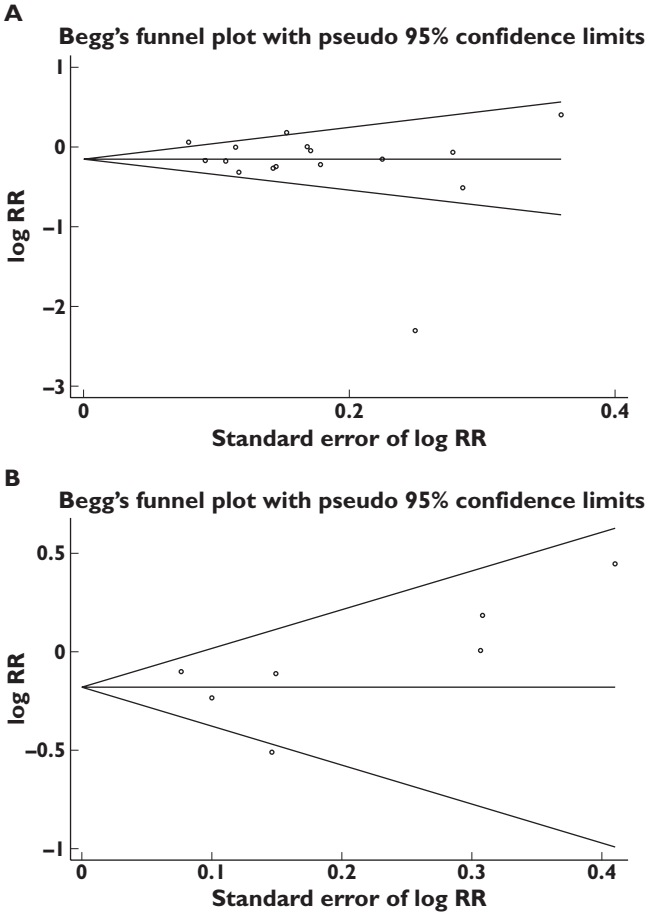

Figure 2

(A) Funnel plots of the relative risk of developing ovarian cancer, with the standard error, for all studies included in the meta-analysis. Relative risks are displayed on a logarithmic scale. The x axis represents standard error of log RR, and the y axis represents log RR. For aspirin use: $P = 0.592$ for the Begg–Mazumdar test; $P = 0.178$ for the Egger test. (B) Funnel plots of the relative risk of developing ovarian cancer, with the standard error, for all studies included in the meta-analysis. Relative risks are displayed on a logarithmic scale. The x axis represents standard error of log RR, and the y axis represents log RR. For non-aspirin-NSAID use: $P = 0.051$ for the Begg–Mazumdar test, $P = 0.125$ for the Egger test

0.98), but not statistically significant based on a random-effects model (RR = 0.89, 95% CI 0.74, 1.08) (Table 2). However, the random-effects model is generally thought to be more appropriate, because it provides a more conservative estimate of the pooled effect size.

To evaluate the consistency across varying study designs with different potential biases, we stratified data into subgroups based on study design. The association was neither statistically significant among cohort studies (random-effects model, RR = 0.89, 95% CI 0.74, 1.08; fixed-effects model, RR = 0.82, 95% CI 0.64, 1.04) nor among case–control studies (random-effects model, RR = 0.97, 95% CI 0.73, 1.28; fixed-effects model, RR = 0.88, 95% CI 0.75, 1.03) (Table 2).

Figure 4 illustrates the RRs and 95% CIs from the individual studies and the pooled results.

To analyze any association between dose of non-aspirin-NSAID used and the risk of ovarian cancer, drug exposure was categorized as 'regular' and 'irregular'. 'Regular use' was the most common and 'irregular' was the least common exposure, as reported in the individual studies (Table 3). Three studies [16, 20, 23] provided results on frequency of non-aspirin-NSAID use. The association between 'regular use' of non-aspirin-NSAID and ovarian cancer was statistically significant based on a fixed-effects model (RR = 1.45, 95% CI 1.07, 1.98, $n = 3$), but not based on a random-effects model (RR = 1.47, 95% CI 0.95, 2.27, $n = 3$) (Table 2). In contrast, 'irregular use' did not cause any reduction in the risk of developing ovarian cancer (fixed-effects model, RR = 0.96, 95% CI 0.69, 1.33, $n = 3$; random-effects model, RR = 0.93, 95% CI 0.49, 1.76, $n = 3$) (Table 2). Thus, there was no difference in the risk of developing ovarian cancer between irregular users and non-users.

To assess any association between duration of non-aspirin-NSAID use and the risk of ovarian cancer, we used the available data from studies with durations of more

Table 2

Meta-analysis results

Aspirin use		Fixed-effects model		Random-effects model		Tests of homogeneity			Tests of publication bias	
	Number of studies	RR	(95% CI)	RR	(95% CI)	Q value (d.f.)	*P* value	I^2	Begg's *P* value	Egger's *P* value
All studies	17	0.94	(0.87, 1.01)	0.91	(0.82, 1.01)	26.6 (16)	0.046	39.8%	0.592	0.178
Case–control studies	14	0.94	(0.87, 1.02)	0.90	(0.79, 1.03)	24.97 (12)	0.015	51.9%	0.502	0.218
Cohort studies	3	0.92	(0.77, 1.09)	0.92	(0.77, 1.10)	1.57 (2)	0.456	0%	1.000	0.683
'Regular use'	7	0.86	(0.73, 1.03)	0.83	(0.65, 1.05)	10.14 (6)	0.119	40.8%	0.548	0.442
'Irregular use'	7	1.07	(0.96, 1.20)	1.07	(0.96, 1.21)	6.02 (6)	0.421	0.4%	0.548	0.538
Duration > 5 years	5	0.91	(0.67, 1.24)	0.89.	(0.63, 1.25)	4.59 (4)	0.332	12.9%	0.806	0.426
Non-aspirin-NSAID use		**Fixed-effects model**		**Random-effects model**		**Tests of homogeneity**			**Tests of publication bias**	
	Number of studies	RR	(95% CI)	RR	(95% CI)	Q value (d.f.)	*P* value	I^2	Begg's *P* value	Egger's *P* value
All studies	7	0.86	(0.76, 0.98)	0.89	(0.74, 1.08)	11 (6)	0.089	45.4%	0.051	0.125
Case–control studies	4	0.88	(0.75, 1.03)	0.97	(0.73, 1.28)	8.20 (3)	0.042	63.4%	0.174	0.001
Cohort studies	3	0.82	(0.64, 1.04)	0.89	(0.74, 1.08)	2.53 (2)	0.283	20.9%	1.000	0.59
'Regular use'	3	1.45	(1.07, 1.98)	1.47	(0.95, 2.27)	3.75 (2)	0.153	46.7%	0.296	0.274
'Irregular use'	3	0.96	(0.69, 1.33)	0.93	(0.49, 1.76)	6.55 (2)	0.038	69.5%	1.000	0.486
Duration > 5 years	3	1.65	(1.13, 2.41)	1.56	(0.92, 2.65)	3.12 (2)	0.210	36.0%	1.000	0.905

RR Relative risk; CI confidence interval; Non-aspirin-NSAIDs non-aspirin non-steroidal anti-inflammatory drugs; d.f. degrees of freedom.

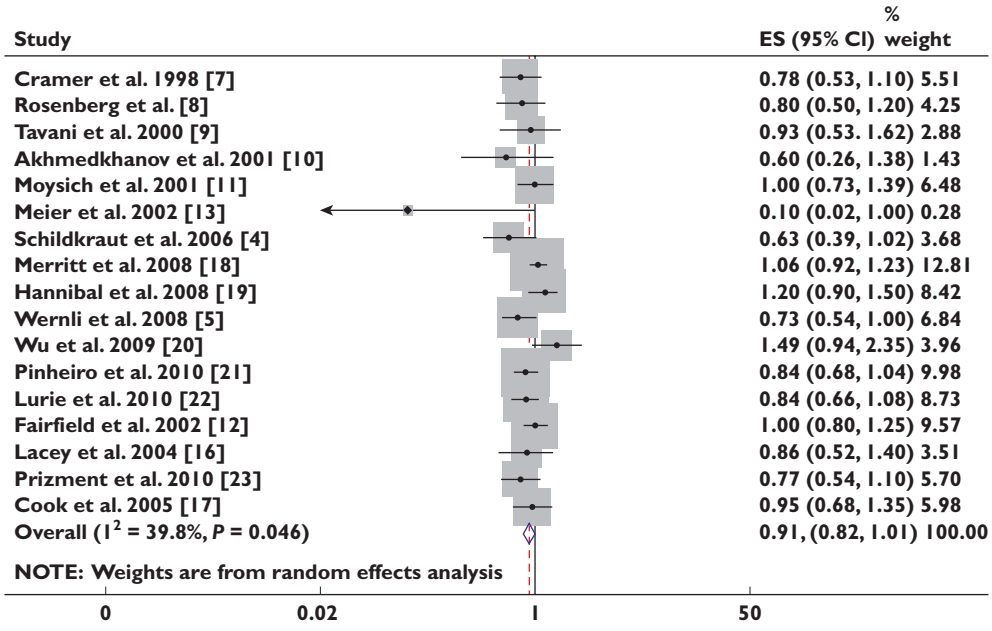

Figure 3

Analysis of studies, listed by first author and publication year that examined ovarian cancer and its association with aspirin use. The relative risk and 95% CI for each study are displayed on a logarithmic scale. Pooled estimates are from a random-effects model

than 5 years. Only three studies [8, 16, 20] were included in this analysis. The association between '>5 years duration of non-aspirin-NSAID' with ovarian cancer was statistically significant based on a fixed-effects model (fixed-effects model, RR = 1.65, 95% CI 1.13, 2.41, $n = 3$), but not based on a random-effects model (RR = 1.56, 95% CI 0.92, 2.65, $n = 3$). However, the number of studies contributing to this analysis was very small ($n = 3$) (Table 2).

Table 3

Definitions of drug use in the studies included in the meta-analysis

Study	Definition of irregular use	Definition of regular use
Aspirin		
Fairfield *et al.* 2002 [12]	1–2 tablets week^{-1}	≥15 tablets per week
Wu *et al.* 2009 [20]	1–7 week^{-1}	>7 week^{-1}
Lacey *et al.* 2004 [16]	≤1 day^{-1}	>1 day^{-1}
Prizment *et al.* 2010 [23]	≤1 time week^{-1}	≥6 times week^{-1}
Moysich *et al.* 2001 [11]	1–6 tablets week^{-1}	≥7 tablets week^{-1}
Schildkraut *et al.* 2006 [4]	<8 times month^{-1} for <3 years	≥8 times month^{-1} for ≥3 years
Merritt *et al.* 2008 [18]	≤1 week^{-1}	≥2 week^{-1}
Non-aspirin-NSAIDs		
Wu *et al.* 2009 [20]	1–7 times week^{-1}	>14 times week^{-1}
Lacey *et al.* 2004 [16]	≤1 day^{-1}	>1 day^{-1}
Prizment *et al.* 2010 [23]	≤1 time week^{-1}	≥6 times week^{-1}

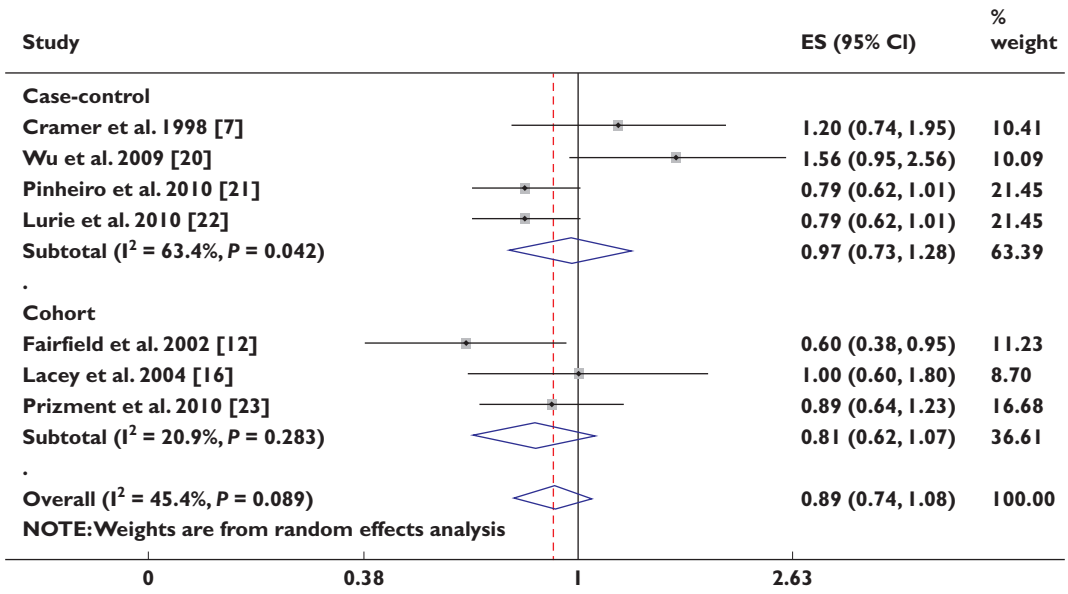

Figure 4

Analysis of studies, listed by first author and publication year that examined ovarian cancer and its association with non-aspirin-NSAID use. The relative risk and 95% CI for each study are displayed on a logarithmic scale. Pooled estimates are from a random-effects model

Discussion

The current interest in aspirin and other NSAIDs as potential agents for the chemoprevention of ovarian cancer stems from the fact that many animal experiments and human epidemiological studies have linked aspirin and other NSAIDs with protective properties in various cancers, including breast, lung, oesophageal, colorectal and prostate cancer. Recent meta-analyses have supported the idea that the overall relative risk of breast [31], lung [32], gastric [33], oesophageal [34] and prostate cancer [35] is reduced in people taking aspirin and other NSAIDs.

However, in this meta-analysis, summary estimates do not support the hypothesis that any use of aspirin is associated with ovarian cancer risk. Contrary to the study hypothesis that NSAIDs may have chemopreventive effects by decreasing inflammation [24], we found that non-aspirin-NSAID use did not decrease the ovarian cancer risk when compared with non-use. However, more studies are needed to confirm our results on non-aspirin-NSAID.

A previous meta-analysis, which was published in 2005, reported no association between NSAID use and the risk of ovarian cancer [24]. However, conflicting results were obtained in the present analysis. This may be attributed to the following reasons: (i) we included one cohort study, seven case–control studies and one clinical trial that were published more recently with inconsistent results [4, 5, 17–23]. Among these studies, four reported a significant

association between ovarian cancer risk and NSAIDs [4, 5, 19, 32], and three reported a RR/OR > 1 [18–20]. (ii) Bonovas *et al*. [24] reported that there was no association between non-aspirin-NSAID use and ovarian cancer risk (fixed-effects model, RR = 0.88, 95% CI 0.76, 1.01, *n* = 6; random-effects model, RR = 0.86, 95% CI 0.68, 1.08, *n* = 6). However, we found a small, potentially significant chemopreventive effect of non-aspirin-NSAID using the fixed-effects model (RR = 0.86, 95% CI 0.76, 0.98, *n* = 7) but no statistically significant difference using the random-effects model (RR = 0.89, 95% CI = 0.74, 1.08). However, the random-effects model is thought to be superior to the fixed-effects model. Therefore, we think that non-aspirin-NSAID use may not be associated with the ovarian cancer risk, but further studies are required to clarify this. We also analyzed the association between dose and duration of non-aspirin-NSAID use and ovarian cancer risk. The association of 'regular use of non-aspirin-NSAID' and 'duration of >5 years of non-aspirin-NSAID' with ovarian cancer was statistically significant when using a fixed-effects model but not when using a random-effects model. There were only three studies included independently with I^2 values of 46.7% and 36% independently, which indicates that our results should be read with caution. In addition, the random-effect model may be superior. Furthermore, whether the frequency or the duration of non-aspirin-NSAID use is the more important factor remains unclear. Therefore, the lowest effective non-aspirin-NSAID dose and the most appropriate duration of use should be further studied. (iii) High heterogeneity was observed in both of the two meta-analyses, and it was not reduced when subgroup analyses were conducted. Aside from the factors analyzed above, other factors such as race, education, family history, menopausal status for women and acetaminophen use may also be responsible for heterogeneity.

Our results on 'regular use of non-aspirin-NSAID' and 'duration > 5 years of non-aspirin-NSAID' with ovarian cancer risk based on the fixed-effects model are similar to the recently reported results reported from the population-based case–control studies conducted by Hannibal *et al*. [19] and Wu *et al*. [20]. In both studies, women were asked to recall prescription and nonprescription medications taken over their lifetime for various conditions. Hannibal *et al*. reported that the risk of ovarian cancer increased significantly in patients with 10+ years of aspirin (RR = 1.6, 95% CI 1.1, 2.2) and non-aspirin-NSAID use (RR = 1.3, 95% CI 1.0, 1.7). However, our results on 'regular use of non-aspirin-NSAID' and 'duration > 5 years of non-aspirin-NSAID' with ovarian cancer risk (based on the fixed-effects model) and those from studies by Hannibal *et al*. [19] and Wu *et al*. [20] differed from most previous studies on this topic. Cramer *et al*. reported a reduction of ovarian cancer risk with a history of using aspirin [7]. However, seven (three case–control, four cohort) of 13 (seven case–control, six cohort) studies have found no significant relationship between the use of NSAIDs and ovarian cancer. The case–control studies showing null findings were conducted in Italy [9], the UK [13] and Australia [18], and they investigated risk associations with use of aspirin [9] and other NSAID [13]. There was also no relationship between cancer risk and use of low dose aspirin [14] and other NSAIDs [15] in a Danish prescription database study. In the Breast Cancer Detection Demonstration Project Follow-up Study (BCDDP), risk was not significantly related to the use of aspirin and other NSAIDs, but risk was increased with 5+ years of use of other NSAIDs (RR = 2.0, 95% CI 0.95, 4.2) [16]. Six other studies (four case–control, two cohort) are supportive of an inverse association with NSAIDs use, four studies found a significant reduction in risk with use of other NSAIDs [4, 5, 11, 12]. However, there were differences in study designs. In one study, an inverse association was only found in nulliparous and non-oral contraceptive users [5]. No dose–response relationship was observed in a second study [12], and information on NSAID use was limited to the 5 years before diagnosis in a third study [4]. Aspirin use was not significantly associated with risk in these five studies [4, 8, 10–12]. NSAID use was heterogeneous in these studies because different NSAIDs were included, the exposure period varied (e.g. adult use, use in previous 20 years or previous 5 years before ovarian cancer diagnosis), and information on frequency and duration of NSAID use was asked in only some studies.

Mechanisms whereby 'regular use of non-aspirin-NSAID' and 'duration > 5 years of non-aspirin-NSAID' may increase risk of ovarian cancer (based on the fixed-effects model) may be partially related to the underlying conditions associated with medication use. Secondly, we cannot rule out the possibility of selective recall bias among ovarian cancer patients. Given that many NSAIDs products are available and use may be episodic, it is conceivable that some patients may be more motivated to remember their NSAID use than control subjects. Thirdly, there is also the possibility of surveillance bias and that certain health conditions led to regular NSAID use, resulting in frequent doctor visits, which increased the chances of ovarian cancer detection. Fourthly, women with early symptoms of undiagnosed ovarian cancer take pain medications to relieve these symptoms. This possibility seems less likely because in the study by Wu *et al*. the increased risk results were essentially unchanged when they excluded participants who initially started using these medications within 5 years of diagnosis.

Several limitations should be considered in interpreting the results of this meta-analysis. First, our search was restricted to studies published in indexed journals. We did not search for unpublished studies or for original data. However, we did not impose any exclusion criteria regarding language, place of publication or quality.

Second, the included studies were different in terms of study design and definitions of drug exposure. We tried to explore sources of heterogeneity conducting several subgroup analyses. However, the summary effect estimates are

based on sparse and heterogeneous data. Similarly, for the non-aspirin NSAIDs, all drugs were regarded as being the same. Pharmacologically, this is not correct and the different drugs have different kinetics and dynamics and therefore may have different effects on risk. Third, the methods used to elicit the exposure differed among the individual studies. Most studies [5, 7, 9–12, 16, 17, 20–23] used personal interviews or self-administered questionnaires that rely on the subject's ability to recall, which has repeatedly been shown to be relatively poor for non-repetitive NSAID use. Fewer studies [13, 15] used automated databases that provided detailed information on dates of use and types of drugs used. Because the information is recorded prospectively, it is equally good for cases and controls irrespective of the event of interest. However, studies that used prescription databases lacked information on over-the-counter use, and were based on the assumption that the amount of NSAIDs dispensed was a good approximation of actual consumption. This may not be true, especially for non-aspirin NSAIDs that are frequently prescribed to be taken only when needed.

Fourth, observational studies lack the experimental random allocation of the intervention necessary to test exposure-outcome hypotheses optimally. Thus, results may have been confounded by several factors, given that each one of the studies included in our meta-analysis controlled for somewhat different confounding factors (Table 1). None of the individual studies adjusted for some factors that may affect the use of these drugs, such as the motivation for NSAID use [36, 37]. For example, aspirin is also used in the primary and secondary prevention of coronary heart disease. We cannot exclude the possibility that earlier mortality among aspirin users (e.g. from heart disease) may preclude diagnosis of ovarian cancer and therefore produce a beneficial effect.

Fifth, the dose–response relationship was evaluated based on regular and irregular intake, which is not very precise and may not be indicative of the lack of dose dependency. Therefore, our results should be interpreted with caution.

Despite the limitations listed above, our analysis shows that there was no strong association between NSAID (aspirin/NA-NSAID) use and ovarian cancer risk.

The finding in this study requires confirmation through further characterization of the association by frequency and duration of use, cumulative dose and timing of exposure. In addition, it will be important to evaluate the underlying conditions for medication use.

Competing interests

The authors declare that they have no conflict of interests.

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